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INJECTABLES and IMPLANTS

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—Injectable Progestogens— Officials Debate But Use Increases

The place of the injectable progestogen in family planning remains uncertain. Although some compounds have been used as injectable contraceptives for over a decade and are both popular and effective, controversy still surrounds them.

Depo-Provera ® (depot medroxyprogesterone acetate), a product of the Upjohn Company, USA, is currently the only injectable progestogen in widespread use; it is available commercially for contraceptive purposes in 64 countries. Another will be available soon. Schering AG of the Federal Republic of Germany is now registering an injectable progestogen, norethindrone enanthate (also known as norethisterone enanthate) in some 70 countries. It will be marketed commercially under the brand name Norigest ® and available for family planning organizations under the brand name Noristerat ®.

Injectable progestogens offer many advantages that may be of special importance in developing countries. They are:

- highly effective in preventing pregnancy, on a par with oral contraceptives.
- independent of coitus.
- simple to administer.
- long-lasting, with injections required only two or four times a year.
- not lactation suppressors and thus, unlike combination oral contraceptives, can be offered to nursing mothers without danger of reducing the supply of milk.
- popular in developing countries where injections are associated with safe, effective, modern medicine.

An estimated 1 million women now depend on injectable progestogens for contraception. That number is small compared with the 50 million who use oral contraceptives and the 15 million who use intrauterine devices (IUDs), but the use of injectables appears to be gradually increasing. In recent years international donors of contraceptive supplies have received a growing number of requests for injectables and several countries have added Depo-Provera to their national family planning programs.

This **Population Report** on injectable progestogen contraceptives was prepared by Ward Rinehart and Jane Winter on the basis of published and unpublished papers, personal interviews, and correspondence.

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The injectable progestogens are not without problems. Over the short run, they disturb menstrual patterns in many women and cannot be immediately withdrawn if other problems arise. Over the long run, the return of fertility after discontinuation may be delayed, especially with Depo-Provera.

Because of suspicions about other long-term effects, the use of Depo-Provera has been limited. In some countries concern about permanent infertility after injections has caused it to be restricted to older women with completed families. In other countries Depo-Provera has not yet won regulatory approval for general use. A controversy in the USA over the interpretation of statistical data on cervical carcinoma *in situ* has prevented approval specifically for contraception. The US Food and Drug Administration (USFDA) is reanalyzing the raw data on cervical carcinoma *in situ*, a possible precursor of invasive cancer. A report is expected in 1975.

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An injectable contraceptive is a welcome addition to family planning methods. But the present progestogen injectables, troubled as they are by menstrual side effects and unresolved questions about long-term effects, have not yet won the unqualified approval of clinicians. Nevertheless, if further research can dispel fears about carcinogenicity and disprove or define the risk of infertility after Depo-Provera use, the injectable progestogens may yet become an important component of family planning programs, especially in areas where treatment by injection is popular.

HISTORY

The first systemic contraceptives, developed in the mid-1950s, were short-acting progestogens administered orally (128). With the development of longer-acting progestogens shortly thereafter, injectable contraceptives also became possible. Over the past 20 years a number of compounds have been tested as injectable contraceptives, but only one—Depo-Provera—is currently being produced for international distribution and is widely used. In the USA, Depo-Provera has a checkered history of regulation and at present is not approved for contraception.

The development of progestogens (synthetic compounds with the effects of the natural hormone progesterone) grew out of the post-World War II competition among drug companies to create synthetic hormones for a variety of therapeutic purposes. These early progestogens are metabolized quickly and therefore have to be administered in frequent small doses in order to maintain their effect. As a result, when in the early 1950s Dr. Gregory Pincus and his associates set about utilizing the powerful ovulation-inhibiting properties of these progestogens for fertility control, they concentrated on developing a contraceptive which could be administered orally.

Dr. Karl Junkmann in 1953 discovered that esterifying a progestogen alcohol created a drug with long lasting effects when injected (20, 62). (Esters are formed from a free alcohol and an acid by the removal of water.) Junkmann and his associates synthesized esters of the progestogen norethindrone, including norethindrone enanthate, in 1958 (63). Medroxyprogesterone acetate was developed by the Upjohn Company at about the same time (6).

Schering AG began clinical studies of norethindrone enanthate (Norigest) in 1957. The major field trials of this drug were conducted in Peru, but other studies have taken place in Egypt, Europe, and elsewhere. In 1967 Norigest was first marketed in Peru, but in 1971 it was withdrawn and field trials suspended pending further analysis of toxicologic findings in rats. Some researchers have since concluded that the findings in rats are not applicable to humans, and Schering AG is now registering Norigest in some 70 countries. The brand name Noristerat will be used when the drug is sold to international donor organizations in order to make it readily identifiable if it should be diverted from intended channels (25).

In 1958 the Upjohn Company began clinical trials of medroxyprogesterone acetate (Depo-Provera) as a treatment for threatened or habitual abortion and for endometriosis. In 1960, the USFDA approved it for these uses on the basis of its safety, but without assessing its effectiveness. In February 1974, after the agency concluded that Depo-Provera had not been proved effective for either of these uses and after steroids administered during pregnancy had been associated with congenital defects (69, 117), the USFDA withdrew its approval for use of Depo-Provera during pregnancy or to treat endometriosis (33, 34, 35).

The first clinical trials of Depo-Provera as a human contraceptive began in 1963 and established a standard regimen of 150 mg every three months. Field trials began in 1965 and have since been conducted in 61 countries (48). Since the late 1960s regimens of 300 or 400 mg every six months have also been studied.

Upjohn applied to the USFDA in 1967 for permission to market Depo-Provera as a contraceptive in the USA (173), but, at first, questions about reversibility and relationship to breast cancer in beagle dogs and, more recently, questions about cervical carcinoma *in situ* in humans have blocked USFDA approval.

In 1972 Depo-Provera received USFDA approval as a palliative treatment of advanced endometrial cancer. Currently this is the only approved use in the USA (168). Depo-Provera has also been studied as a treatment for idiopathic precocious puberty (64, 83, 106), but its effectiveness and safety for this purpose have not been established.

Several combinations of a progestogen and an estrogen are being distributed in a few countries as monthly injectables. Promeco markets the combination of algestone acetophenide and estradiol enanthate in Mexico and Argentina under the brand name Perlutal® and in Spain under the brand name Topasel®. In Chile, Recalcine Laboratories produces Aguria®, and Silesia Laboratories produces Unalmes®. Both are combinations of dihydroxyprogesterone acetophenide and estradiol enanthate.

Other steroids have also been tested as injectable contraceptives, but are not being pursued because of the expense of clinical trials needed to prove safety (130) and/or the severe disturbances of the menstrual cycle which they produced (67, 74, 109). These other injectables include Deladroxate ®, developed by E. R. Squibb & Sons, USA, which was a combination of dihydroxyprogesterone acetophenone and estradiol enanthate, for monthly injection; chlormadinone acetate, manufactured by E. Merck-Darmstadt, FRG; and hydroxyprogesterone caproate, manufactured by Schering as Prolutin Depot® and marketed by Squibb as Delalutin®. A few trials have also been con-

Fig. 1. A woman receives an injection of Depo-Provera from a nurse at the McCormick Hospital Family Planning Clinic, Chiang Mai, Thailand. (Courtesy of Dr. E. B. McDaniel.)

ducted combining Depo-Provera with estradiol cypionate (17, 78, 153), Norigest with estradiol undecylate (66), norgestrel with estradiol benzoate (21), and utilizing the estrogen estradiol undecylate alone (28, 67).

Recent interest in progestogen-only contraceptives represents a return to the intentions of early researchers in steroidal contraception. They originally envisioned oral contraceptives as pure progestogens but then discovered that small amounts of estrogen, present as contaminants, reduced the breakthrough bleeding caused by the progestogens. As a result, manufacturers added controlled amounts of different estrogens to the pills (77). Estrogen, however, may cause annoying side effects such as nausea, dizziness, and breast tenderness (22) as well as other, more serious conditions (55). To avoid estrogens, investigators in the late 1960s turned their attention back to progestogen-only formulations—in the form of either oral "minipills" or injectables.

MECHANISM OF ACTION

The injectable progestogens prevent pregnancy in much the same way that combined oral contraceptives do, and with the same high degree of effectiveness, by

- inhibiting ovulation in many women
- increasing the viscosity of cervical mucus, thus forming a barrier to spermatozoa
- changing the rate of ovum transport through the oviducts
- making the endometrium less suitable for implantation.

The contraceptive effect of Depo-Provera depends primarily on its ability to stop ovulation. Norigest works largely by altering cervical mucus (72, 74). After the first six to eight weeks, women using Norigest often do ovulate (4, 7, 73). The two injectables differ slightly in their effects, possibly because they are derived from different sources. Norethindrone enanthate, like most progestogens currently used in oral contraceptives, is derived from 19-nortestosterone, which is structurally similar to testosterone. Medroxyprogesterone acetate, on the other hand, is structurally similar to progesterone.

Progestogens probably affect ovulation by acting on the hypothalamus-pituitary axis, causing suppression of the surge of luteinizing hormone (LH) normally seen at midcycle just prior to ovulation (38, 42, 74, 108, 112, 131, 139, 161). Without that surge ovulation does not take place.

The injectable progestogens make cervical mucus scant, viscous, and sticky, as it is during pregnancy and during the infertile late portion of the menstrual cycle (4, 29, 112, 131, 184). This mucus interferes with the movement of sperm into the uterus. Post-coital tests have shown that some sperm penetrate the viscous cervical mucus but rarely reach the uterine cavity or the oviducts (29, 70, 71, 181, 188). With Norigest changes in cervical mucus appear during the first month after the first injection (29). With Depo-Provera, changes appear during the second month (30).

Under progestogen contraception, the endometrium becomes unable to support a fertilized ovum. With Depo-Provera, the endometrium takes on a resting or atrophic appearance which becomes more apparent as use continues (30, 112). With Norigest the effects vary. In some cases the endometrium resumes normal cyclic changes during the second month after an injection (20, 74). In other cases it may remain unsuitable for implantation throughout Norigest use (4, 29). Both injectables also appear to cause changes in the oviducts, interfering with ovum transport and/or sperm capacitation and transport (12, 30, 184).

EFFECTIVENESS

The standard regimens of Depo-Provera and Norigest offer highly effective protection against pregnancy. Among

Fig. 2. Advertisements for Depo-Provera in several languages reflect widespread use of the injectable. (Courtesy of the Upjohn Company.)

women receiving injections of 150 mg Depo-Provera at 90-day intervals or 200 mg Norigest at 84-day (12-week) intervals, fewer than one in a hundred women are likely to become pregnant during a one-year period (see Tables 1 and 2). The injectables are as effective in preventing pregnancy as combined estrogen-progestogen pills, slightly more effective than progestogen-only "minipills," and markedly more effective than IUDs.

Data on the effectiveness of the 150 mg/3 month regimen of Depo-Provera shown in Table 1 represent over 20,000 woman-years of experience with the drug. Less extensive studies using 300 or 400 mg Depo-Provera at six-month intervals have also been conducted (see Tables 1 and 2).

There are not as many published studies of Norigest as of Depo-Provera (150 mg/3 months), but the pregnancy rates reported for women using Norigest appear to be slightly higher (see Table 1). With both drugs, most accidental pregnancies occur either shortly after the first injection, before the drug has fully taken effect, or just before the end of an injection interval when its effect has begun to wear off (74, 78, 81, 136). Some failures have also been attributed to injections which were not administered deep in the deltoid or gluteal muscle as required (186).

SHORT-TERM SIDE EFFECTS

Though highly effective and easy to administer, the injectable progestogens are not without problems. In the short

Table 1—Effectiveness of Injectable Progestogen Contraceptives in Selected Studies, 1967-1975

Author & Date of Publication	Reference Number	Area	Number of Patients	Number of Woman-Months	Number of Pregnancies	Method Failure Rate[a]
		Depo-Provera (150 mg/3 months)				
Apelo *et al.* 1974	3	Philippines	226	5,109	0	0
Bloch 1971	9	South Africa	7,335	38,714	11	.35
Brat 1971	11	Belgium	584	4,677	3	.77
Chinnatamby 1971	16	Sri Lanka	1,000	18,261	3	.02
Dodds 1971	23	Hong Kong	1,883	30,734	1	.04
El-Mahgoub *et al.* 1972	27	Egypt	231	4,671	0	0
Koetsawang *et al.* 1974	81	Thailand	886	24,399	25	1.2
Leiman 1972	87	South Africa	1,507	12,819	1	.09
Linthorst *et al.* 1972	88	Netherlands	690	5,009	3	.72
Mishell *et al.* 1971[b]	111	USA	312	5,377	0	0
Nunez 1970	122	Honduras	250	2,490	1	.48
Powell & Seymour 1971	129	USA	1,123	14,001	1	.09
Schwallie & Assenzo 1973	150	USA & Latin America	3,857	72,215	15	.25
Scutchfield *et al.* 1971	154	USA	650	4,958.5	1	.23
Soichet 1969[b]	157	USA	298	4,128	1	.29
Tyler 1970[b]	166	USA	214	2,514	0	0
Zanartu & Onetto 1972[b]	186	Chile	561	22,000	4	.25
Zartman 1967[b]	189	USA	480	4,528	0	0
		Norigest (200 mg)[c]				
Chinnatamby 1971	15	Sri Lanka	520	4,391	9	2.3
El-Mahgoub & Karim 1972	29	Egypt	171	4,329	0	0
Kesseru-Koos *et al.* 1973	74	Peru	2,177	21,730	16	.88
Koetsawang 1975	78	Thailand	71	648	8	14.8
Rice-Wray *et al.* 1971	136	Mexico	112	1,069[d] 308	0 0	0 0
Zanartu & Onetto 1972	186	Chile	130[d]	2,300	10	5.2
		Depo-Provera (6 months)[e]				
El-Mahgoub *et al.* 1972	31	Egypt	92	904	0	0
Khan *et al.* 1973	76	Pakistan	145	1,673.5	5	3.6
Mackay *et al.* 1971	105	Australia	61	989	0	0
Nunez 1971	123	Honduras	300	2,385	1	.5
Schwallie & Assenzo 1972	149	USA & Latin America	991	21,470	31	1.73
Zanartu & Onetto 1972	186	Chile	1,099[f] 598[g]	43,387 20,387	54 28	1.4 1.6

[a]Calculated by Pearl formula (pregnancies per 100 woman-years of use).
[b]Participated in Upjohn cooperative study. Data on all women (except Soichet 1969 (157), 51 women) also reported by Schwallie & Assenzo 1973 (150).
[c]Injection interval was 84 days except as noted. [d]Injection interval was 90 days. [e]Dose was 300 mg except as noted.
[f]Dose was 250 mg. [g]Data also reported by Schwallie & Assenzo 1972 (149).

run, they frequently disturb menstrual patterns, sometimes severely, and Depo-Provera may also cause weight gain.

Menstrual Cycle Disruptions

All progestogens, but especially the injectables, disrupt menstrual patterns. Women using injectables may experience shorter or longer cycles, increased or decreased menstrual flow, and spotting. Many women tolerate these disturbances, but others do not. Menstrual disturbances cause more women to discontinue injectables than does any other side effect. Therefore, supplemental estrogens are sometimes used to regulate menstruation.

The injectables have their most unpredictable effects on menstrual patterns during the first months of use. Discernible menstrual cycles may disappear entirely, to be replaced by intermittent bleeding and spotting of unpredictable duration, interval, and rate of flow. If identifiable cycles continue, their length may vary widely from month to month and from one woman to another. In a few women, injectables immediately bring on amenorrhea. In many Depo-Provera studies fewer than half the users experienced "normal" menstrual flow following a first injection (2, 23, 81, 101, 149, 150). Irregular bleeding often gives way to amenorrhea which may then continue as long as the drug is used. By the end of two years, 40 percent or more of Depo-Provera users may be amenorrheic (23, 81) (see Fig. 3).

Researchers who have studied both injectables suggest that Norigest disturbs menstrual patterns less than Depo-Provera (29, 74, 185). But comparing separate studies of the two injectables is difficult because of differing definitions of normal menstrual patterns and differing methods of aggregating data. While more and more Depo-Provera users experience amenorrhea as usage continues, Norigest users appear to experience an increasing proportion of normal cycles as time passes (29, 144) (see Fig. 4). This observation may be biased, however, by the fact that

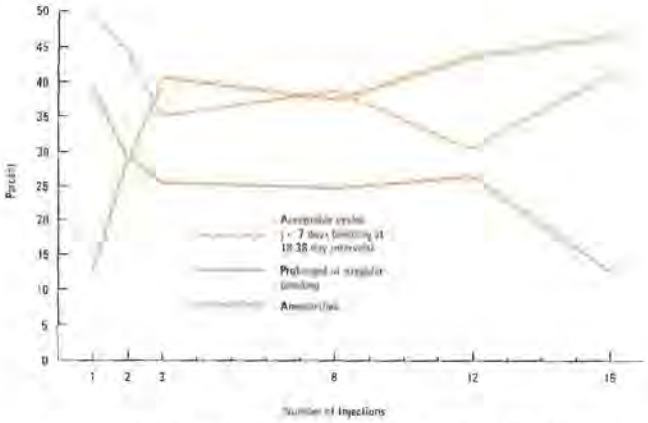

Fig. 3. Percentages of women experiencing various bleeding patterns while receiving three-month injections of Depo-Provera (150 mg).
SOURCE: Adapted from Koetsawang *et al.* (81).

women with disrupted menstrual patterns are more likely to abandon the method than are women with normal cycles.

Management of Bleeding

Orally administered estrogens are often used to treat menstrual disturbances caused by injectable progestogens. At first the estrogens suppress menstrual bleeding. Then, when they are withdrawn and estrogen levels drop, withdrawal bleeding, which may be similar to normal menses, usually occurs. Thus, cyclic administration of estrogens can be used to treat excessive bleeding, irregular bleeding, or amenorrhea.

Various estrogens have been used in different regimens, ranging from a full cycle of oral contraceptives (23) to a single 10 mg injection of long lasting (depot) estrogen (93, 136) to 1 mg or less of oral estrogen daily for several days each month (9, 24, 29, 67, 84, 91, 101, 122, 129, 136, 154, 184). Supplemental estrogens have been adminis-

Table 2—Effectiveness of Depo-Provera in Selected Studies by Life Table Method[1], 1972-1974

Author & Date of Publication	Reference Number	Area	Number of Women Starting Use		Pregnancies per 100 women				
					Year 1	Year 2	Year 3	Year 4	Year 5
THREE MONTH DOSE (150 mg)									
McDaniel *et al.* 1974	103	Thailand	9,284	In Each Year:	1.0	.4	0		
				Cumulative:	1.0	1.4	1.4		
Schwallie & Assenzo 1973	150	USA & Latin America	3,857	In Each Year:	.31	.26	.37	0	0
				Cumulative	.31	.53	.90	.90	.90
Zanartu & Onetto 1972	186	Chile	561	In Each Year:	.5	.3	0	0	
				Cumulative:	.5	.8	.8	.8	
SIX MONTH DOSE									
McDaniel & Pardthaisong 1974 (400 mg)	101	Thailand	1,132	In Each Year:	.7	.9	.8	.2	.6
				Cumulative:	.7	1.6	2.4	2.6	3.2
Schwallie & Assenzo 1972 (300 mg)	149	USA & Latin America	991	In Each Year:	2.28	1.34	1.06	.57	
				Cumulative:	2.28	3.62	4.68	5.25	
Zanartu & Onetto 1972 (300 mg)	186	Chile	598	In Each Year:	1.8	1.3	1.2	.6	
				Cumulative:	1.8	3.1	4.3	4.9	

[1]The life table method measures pregnancy rates per 100 women in a specified time period of contraceptive use.

tered either routinely, in response to a patient's request or complaint, or when indicated by objective criteria such as heavy bleeding. McDaniel has suggested the following indications for the use of supplemental estrogens with Depo-Provera:

- prolonged spotting (more than 7 days in 28)
- heavy bleeding (more than was usual before injections began)
- more than 7 days bleeding
- any bleeding which is or could become a source of progressive anemia
- three or more months of amenorrhea, if it is disturbing to the woman (91).

Other conditions, such as pelvic infection, cervicitis, malignancies, moniliasis, or tricomoniasis, may also produce menstrual disruption. Clinicians should therefore ensure that these conditions are absent before blaming the injectable (9).

Although he has suggested specific indications for the use of supplemental estrogens, McDaniel himself administers them routinely to all his patients in the McCormick Hospital Family Planning Program in Chiang Mai Province, Thailand. He does so in an attempt to provide women with the reassurance of at least one withdrawal bleeding between injections and to prevent the rare occurrences of heavy bleeding which would require immediate medical care difficult to obtain in rural areas (52).

If oral estrogens are used in conjunction with injectable progestogens, some women may consider the method not much more convenient than taking standard oral contraceptives (24, 67). This objection may be largely overcome by the administration of a single dose of long acting oral estrogen, such as quinestrol, given monthly or at the time of injection, as is currently done in the McCormick Hospital program (94). Despite the fact that estrogens sometimes cause side effects such as nausea and dizziness, the advantages of a regular menstrual pattern outweigh the disadvantages of estrogenic side effects for some women (155). Also, the advantages of complete protection for a three-month interval may outweigh the apparent inconvenience of using both oral medication and injections. Furthermore, the woman who fails to take her oral estrogen supplement does not increase the risk of pregnancy as does the woman who fails to take an oral contraceptive tablet (24, 91).

Several researchers have studied either Depo-Provera or Norigest combined with a long-lasting injectable (depot) estrogen—for example, 25 mg medroxyprogesterone acetate with 5 mg estradiol cypionate (17, 78) or 50 mg norethindrone enanthate with 5 mg estradiol undecylate (66). These combination injectables, administered monthly, produce fewer menstrual pattern disturbances than the higher-dose, longer-lasting progestogens alone. No pregnancies have been reported with these combinations, but experience is still very limited.

Weight Gain

Weight gain, which may be an advantage to some and a disadvantage to others, occurs in a majority of Depo-Provera users (2, 46, 87, 122, 141, 155). In clinical studies mean weight gain has ranged from 1.4 pounds (141) to 9 pounds (155) in the first year of Depo-Provera use. Some

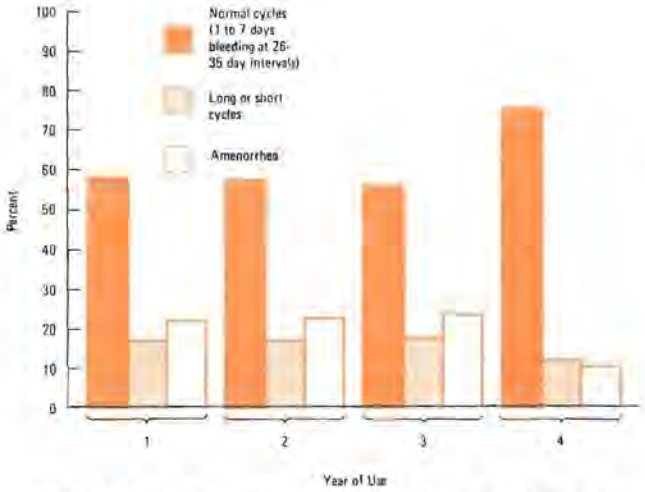

Fig. 4. Percentages of menstrual cycles of various types in Peruvian Norigest users with previously normal menstrual patterns, by year of Norigest use.
SOURCE: Adapted from Schering AG (145).

researchers find that weight gain levels off after the first year (15, 46, 190). Others report a slow and continuing increase (141, 150). McDaniel *et al.*, studying 800 Thai women who used Depo-Provera for 30 months, found that mean weight gain at the end of 12 months was 2.8 pounds; at 24 months, 5.1 pounds; and at 30 months, 5.4 pounds (103). Which women will be affected is not predictable, although obese women may gain less than others (87).

In some parts of the world weight gain is actually an asset (3, 16). Apelo *et al.* report from the Philippines that:

> Weight gain did not prove to be a problem because this was usually welcomed by most women, especially those who belonged to the lower socioeconomic group. A gain in weight, to them, connoted tolerance to the drug and they felt happy about it (3).

Carbohydrate Metabolism

Depo-Provera may have some effect on carbohydrate metabolism, although this relationship has not been definitely established. Some researchers find that Depo-Provera raises glucose levels in the blood (13, 39, 114, 160); others report that it does not (30, 150, 165, 167, 171).

The clinical issue at stake in the debate over carbohydrate metabolism is whether diabetics and pre-diabetics should use Depo-Provera. If Depo-Provera does raise blood glucose levels, diabetics and pre-diabetics may not be able to produce the additional insulin necessary to metabolize the extra glucose (39). Since diabetics and pre-diabetics face higher risks during pregnancy, their need for effective contraception is great. Close medical supervision during their use of contraception is necessary.

Progestogen-only minipills do not seem to interfere with carbohydrate metabolism (133). No changes in carbohydrate metabolism have been reported in women using Norigest (29, 40, 184).

Other Side Effects

Other complaints reported by users of injectables include nausea, dizziness, headache, nervousness, chills, change in skin pigmentation, galactorrhea, painful menstruation, lessening of libido, diminished orgasm, and acne. How

often nonmenstrual side effects occur and what proportion of users experience these often highly subjective symptoms vary from one study to the next. In the Upjohn Company's cooperative studies of Depo-Provera, Schwallie and Assenzo reported that nonmenstrual side effects other than weight gain were similar in type and frequency to those reported by users of oral contraceptives (149, 150). On the other hand, Scutchfield and his associates found that, in a Georgia (USA) family planning clinic, the side effects among Depo-Provera users paralleled those of IUD users rather than those of orals users (154). Larranaga and Kesseru have commented that there are fewer nonmenstrual side effects with Norigest than with orals (86). Injectables might be expected to cause fewer nonmenstrual side effects because they do not contain estrogen, which has been blamed for nausea, dizziness, and headache associated with combination oral contraceptives (22).

With the possible exception of weight gain in Depo-Provera users, clinicians have not observed symptoms of metabolic or endocrine changes among users of injectables. Most field trials have yielded no clinical evidence that the injectables adversely affect blood clotting, adrenal or liver function, blood pressure, or lactation, all of which are affected to some degree by estrogen-progestogen contraceptives. Nor have laboratory studies produced any conclusive evidence of adverse metabolic or endocrine effects.

CONTINUATION

Despite the side effects of injectables, 60 percent or more of all users can be expected to continue with the method for at least one year (see Table 3). Continuation rates are influenced not only by the characteristics of the contraceptive method but also by the age and parity of the user, social and cultural attitudes, accessibility of services, availability of alternate methods, and other factors. Therefore, comparisons among studies are difficult to make. Researchers who have compared continuation rates for different contraceptive methods in similar patient populations have found that the continuation rate for Depo-Provera was higher than that for orals but lower than that for IUDs (3, 95, 154) (see Fig. 5). Doctors at a clinic in Egypt report that the continuation rate for Norigest was higher there than rates both for IUDs and for orals (29).

Among side effects of Depo-Provera, excessive and irregular menstrual bleeding or spotting can be blamed for the largest proportion of discontinuations—between one-quarter and one-half of all first-year drop outs. Amenorrhea is responsible for about 10 percent of discontinuations (see Table 4). Menstrual disturbances caused by Norigest, because they are less severe than those due to Depo-Provera, apparently cause fewer discontinuations, though reports are few. In the Peruvian field trials of Norigest, by the end of two years 5.5 percent had dropped out because of menstrual disturbances, most of that in the first year. Some 87 women discontinued Norigest because of amenorrhea; 15, because of spotting or breakthrough bleeding (74).

Women may find menstrual disturbances upsetting because they think that irregular or excessive bleeding is a symptom of sickness or that amenorrhea is a sign of pregnancy. Religious practices, folk beliefs, and rumors may also contribute to a woman's concern. For example, in Egypt, investigators have reported that:

Table 3—Percentage of Women Continuing Use of Depo-Provera or Norigest by Months of Use in Selected Studies, 1970-1974

Author & Date	Reference Number	Country	Number of Women	Dose Interval in Months	Percentage of Women Receiving Next Injection by Months of Use									
					3	6	9	12	15	18	24	36	48	60
DEPO-PROVERA:														
Apelo *et al.* 1974	3	Philippines	226	3	92	81		72		63	60			
Dodds 1971	23	Hong Kong	1,883	3				61			48			
Khan *et al.* 1973	76	Pakistan	145	6		54		41		34	26			
Koetsawang *et al.* 1974	81	Thailand	886	3				76			60	46	38	
McDaniel *et al.* 1974	103	Thailand	9,284	3				74			59	48		
McDaniel & Pardthaisong 1974	101	Thailand	1,132	6				86			78	67	55	46
McDaniel & Pardthaisong 1973	102	Thailand	217	3	79	69	64	60						
			108	6		69		60						
McDaniel & Pardthaisong 1972	95	Thailand	2,967	3	89	78	69	62	55	48				
Schwallie & Assenzo 1973	150	USA & Latin America	3,857	3				59			42	30	24	22
Schwallie & Assenzo 1972	149	USA & Latin America	991	6				67			42	27	14	
Scutchfield 1971	154	USA	723	3		76		57		49				
Sin *et al.* 1973	156	Malaysia	550	1-6				63			41			
Zartman 1970	190	USA	478	3	93						77			
NORIGEST:														
Kesseru-Koos *et al.* 1973	74	Peru	1,844	84 days		86		75		69	66			

> For many women this unpredictable menstrual behavior was disturbing as they feared that amenorrhea may indicate pregnancy or they believe that retention of menstrual blood has a serious toxic effect on the body. Spotting is troublesome as it compels our cases to prohibit intercourse due to religious habits; mild or excessive bleeding is most alarming (67).

Bantu women believe that amenorrhea means blood will collect in the head, causing headaches (68). In Chiang Mai Province, Thailand, the rumor once circulated that amenorrhea leads to insanity (95).

If such fears can be eliminated, many women will tolerate amenorrhea. That a woman's psychological well-being depends on regular menstruation may be, as Molitor puts it, "a somewhat masculine idea" ("une idee un peu masculine") (113). Poor nutrition and short birth intervals in developing countries may make regular menstrual patterns the exception rather than the rule. Clinicians from various areas report that many women actually are pleased by the absence of menstruation (81, 84, 113).

Educating and reassuring women about menstrual disturbances can promote continuation of the method. In Mexico, Rice-Wray and her associates

> have found that the continuation rate depends largely on the confidence the patient has in the doctor and the explanation she received (136).

Zanartu, in Chile, has recommended group instruction about menstrual disturbances (186), and Chinnatamby, from Sri Lanka, has stressed the importance of repeated assurances (16).

Among nonmenstrual side effects of Depo-Provera, weight gain is sometimes a reason for discontinuation, but, because the gain usually is moderate, it is not a major cause of dropouts. For example, in the Upjohn Company's cooperative studies, involving mainly US women, it caused only 1.7 percent of the participants to discontinue (149).

Various other nonmenstrual symptoms, including those subjectively determined, are responsible for a small proportion of discontinuations among users of injectables. Only 1.1 percent of the women in the Peruvian field trials abandoned Norigest because of nonmenstrual side effects (74). In most large studies of Depo-Provera, less than six percent discontinued because of nonmenstrual complaints other than weight gain (16, 81, 104, 149, 150).

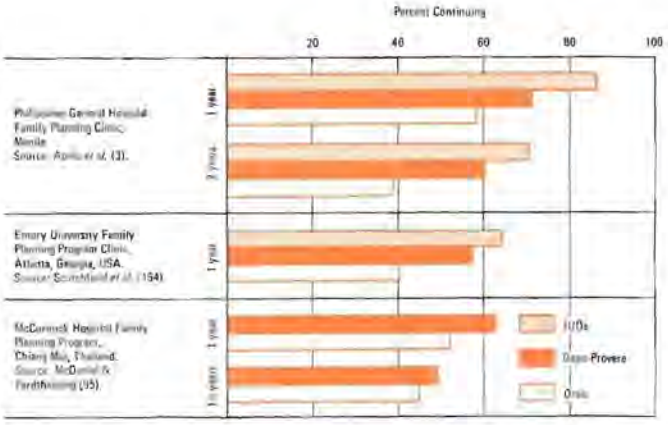

Fig. 5. Percentages of women continuing various contraceptive methods in three clinic programs, 1971-1974.

FERTILITY-RELATED EFFECTS

Return of fertility may be delayed for several months or longer after discontinuing use of an injectable. This effect is more frequent and longer lasting with Depo-Provera than with Norigest. In addition, various progestogens may be associated with virilization and an increase in congenital defects among the offspring of women who receive the drugs during early pregnancy.

Return of Fertility

A study of 114 women who discontinued Depo-Provera in order to become pregnant showed that median time to

Table 4—Percentage of Women Discontinuing Use of Depo-Provera for Menstrual Disturbances by Years of Use in Selected Studies, 1970-1973

Author & Date of Publication	Reference Number	Country	Number of Women Starting Depo-Provera	Percentage Discontinuing					
				For Amenorrhea		For Excess or Irregular Bleeding		For All Reasons	
				1 year	2 years	1 year	2 years	1 year	2 years
Dodds 1971	23	Hong Kong	1,883	6	9	13	17	39	52
Jeppsson 1972	61	Sweden	139	2		14		42	
Khan *et al.* 1973	76	Pakistan	145			24	24	59	74
McDaniel & Pardthaisong 1973	102	Thailand							
3 month regimen			217[a]	2		7		40	
6 month regimen			108[a]	7		10		40	
Scutchfield *et al.* 1971	154	USA	723	3		14		43	
Sin *et al.* 1973	156	Malaysia	550		35		20		59
Zartman 1970	190	USA	478		1		4		23

[a]Postpartum women. Routine estrogen supplement administered after weaning of the infant—usually at 9-12 months.

conception was 13 months from the date of the last 150 mg injection, or 10 months from the assumed end of contraceptive protection. By comparison, median time to conception after discontinuing IUD or diaphram contraception is two months. However, by 18 months after discontinuation cumulative conception rates become similar regardless of the method previously used (151) (see Fig. 6). McDaniel, using 15 weeks after the last injection as the discontinuation point, reported that 76.8 percent of 135 women were pregnant within one year (97). He compared this to one year cumulative conception rates of 94 percent for oral contraceptives (142) and 88 percent for IUDs (162). By 14 months, 82 percent of the former users of Depo-Provera were pregnant.

Fertility returns more quickly after Norigest use. Zanartu has estimated that conception is likely to occur three to six months after the last Norigest injection (182, 183). A study of 48 women who discontinued Norigest found that 15, or 31.3 percent, became pregnant within six months after the last injection (74). While a quicker return of fertility may make Norigest more acceptable than Depo-Provera for a woman who wants more children, it may also mean an unplanned pregnancy for a woman who is even a few days late receiving her next injection.

The duration of infertility after discontinuation of Depo-Provera apparently bears no relationship to the length of time the injectable is used (23, 95, 150, 151), but rather may reflect individual differences in the rate of drug absorption and excretion (151, 174). Women with lower body weights tend to conceive sooner after discontinuing Depo-Provera (151).

Suspicion that Depo-Provera may cause permanent infertility has been a major impediment to its wider use. But, despite the importance of the issue, little research has been conducted on it, possibly because of the difficulty of confirming infertility or determining its causes. Thus, it is not possible to estimate what percentage of women may be affected or even to state firmly that Depo-Provera does cause infertility. Ovulation-stimulating drugs have been used successfully to return fertility after Depo-Provera injections (140), implying that no damage to the reproductive system had occurred.

Fetal Effects

In the late 1950s and early 1960s researchers discovered that some progestogens, when given in early pregnancy, occasionally cause masculinization of the external genitalia of female fetuses (1, 127, 179). In most of these cases, progestogens were given in large doses to prevent threatened or habitual abortion. In large doses medroxyprogesterone acetate (the active ingredient in Depo-Provera) virilizes rat and rabbit fetuses (107, 127), but no such effect on human fetuses has been reported, either with doses of Depo-Provera as high as 400 mg (41) or with Norigest.

Recent reports have suggested that in a few women steroids administered in early pregnancy may cause congenital anomalies. Progestogens administered for pregnancy tests are especially implicated (60, 69, 117, 118, 119, 120). The risk is small—probably no greater than 7 per 10,000 births (85)—and probably occurs only in conjunction with "some type of maternal predisposition" (118). In an attempt to avoid administration during pregnancy, the first injection of Depo-Provera or Norigest is usually given within a few days after menstruation.

DEBATE OVER CANCER RISKS

Suspicion that Depo-Provera might stimulate certain cancers has repeatedly delayed approval of the drug in the USA. A controversy over whether the injectable increases the incidence of cervical carcinoma *in situ*, a possible precursor of invasive cancer, is still unresolved. Several years ago researchers found that both Depo-Provera and Norigest produce breast nodules in certain test animals. Subsequently, however, many scientists have concluded that the results of these animal studies cannot be extrapolated to humans.

Cervical Carcinoma *in Situ*

Some statistics suggest, but do not prove, that cervical carcinoma *in situ* may occur more often among Depo-Provera users than among nonusers. Among 10,333 women who used the injectable for a total of 14,891 woman-years, 35 cases of carcinoma *in situ* were reported (152), but because there was no control group in this study, it is difficult to evaluate these data (44).

An attempt has been made to compare the rates found among Depo-Provera users with age and race adjusted

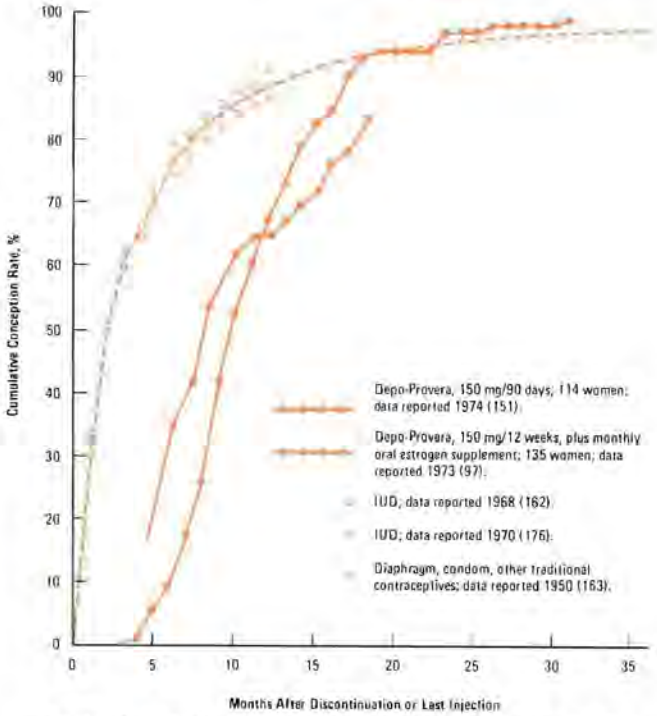

Fig. 6. Cumulative conception rates for women who discontinued Depo-Provera to become pregnant, compared with cumulative conception rates for former users of IUDs and of traditional contraceptives.
SOURCE: Adapted from Schwallie & Assenzo (151).

carcinoma *in situ* rates from US surveys conducted by the National Cancer Institute (NCI) (152). Such a comparison between separate studies, however, leaves a wide margin for possible inconsistency and bias. Depending on the age, race, location, regimen, and, to a lesser extent, the statistical method used, rates of cervical carcinoma *in situ* among Depo-Provera users range from less than one to more than nine times the age and race adjusted rates in the U.S. population (37, 152). For the usual regimen of 150 mg/3 months, the risk is 1.55 times the adjusted US rate (152), a difference which is "statistically and clinically insignificant" (44).

USFDA officials, faced with the problem of how to interpret the inconclusive statistics, twice nearly approved Depo-Provera for contraceptive use and twice withheld approval because of objections from Representative L. H. Fountain, chairman of a congressional subcommittee concerned with intergovernmental relations. It was Fountain who, in 1974, first made an issue of the apparently higher incidence of carcinoma *in situ* among users of Depo-Provera. He has argued that the statistics raise enough doubts about the safety of the injectable to justify keeping it off the market (37).

Responding to Fountain's objections, the USFDA examined the data, and it concluded that no increased risk could be proved. The agency pointed out that almost all of the carcinoma *in situ* cases among Depo-Provera users occurred within the first two years of drug use:

> From all that we know about carcinogenesis, . . . such early tumors cannot be considered as drug related; the absence of a lag time of 3 to 10 years or more is at variance with the known toxicological behavior of chemical carcinogens (146).

The USFDA also argued that the statistics about Depo-Provera raise no more concern than has been raised about the possible carcinogenicity of oral steroidal contraceptives already marketed with USFDA approval (146, 147). Despite these arguments, further protests from Fountain led to another postponement of USFDA approval, which, as of March 1975, remains in effect. The agency will hold an open hearing in April 1975 to discuss the carcinoma *in situ* issue with experts on "contraception, epidemiology, and carcinogenesis" (147).

Only two studies of cervical malignancies among Depo-Provera users have been conducted with control groups for reliable comparisons, and both were too small to be statistically significant. A Chilean study found no difference in the rates at which cervical growths occurred in Depo-Provera users and in IUD users. But, for unknown reasons, women who chose the injectable were more likely to have a cervical malignancy *before* beginning contraception than were those who chose the IUD (18). In a Belgian study which included Depo-Provera, abnormalities and malignancies, as determined by Papanicoulau cervical smears, occurred less than half as often among the users of continuous progestogen contraception as in a control group using no hormonal contraception (54).

Papanicoulau smears taken during the Peruvian field trials of Norigest produced no evidence that the injectable increased the incidence of cervico-vaginal abnormalities (75).

It has been hypothesized that continuous progestogen contraception would be more likely to stimulate carcinogenesis than cyclical combined estrogen-progestogen contraception because an unchanging hormonal environment might encourage mutant cells to multiply unchecked, whereas a changing hormonal environment might check this growth (124, 135). This has not been proved, however.

Breast Nodules and Cancer

Depo-Provera causes breast nodules in beagles. Norigest causes breast nodules in rats and mice, as do other nortestosterone derivatives. But no evidence suggests that the injectable progestogens have the same effect in women, and the applicability of the animal study results to humans is disputed.

Studies conducted by the USFDA in the late 1960s found that female beagles receiving the body weight equivalent of the human contraceptive dose of Depo-Provera developed persistent breast nodules (175) and beagles receiving 25 times the equivalent human dose developed malignant nodules and metastases (36). As a result, in 1970 the Upjohn Company withdrew from the market Provest, a combination oral contraceptive which contained medroxyprogesterone acetate. Chlormadinone acetate, another progesterone derivative studied as an injectable and at the time used in some oral contraceptives, was also removed from the market because it had a similar effect. The USFDA allowed clinical trials of Depo-Provera to continue, however, reasoning that other effective oral contraceptives were available but that Depo-Provera appeared to be the only highly effective injectable (8, 36).

The results of the beagle studies renewed the ongoing controversy over the extrapolation of animal study results to humans. Some researchers argue that dogs, particularly beagles, react differently and are more sensitive to progesterone and progestogens than are women and usually develop a type of breast nodule rarely found in women (14, 115, 116, 169, 175). They also point out that primates given Depo-Provera have not developed breast nodules, to which the USFDA replies that monkeys are more resistant to breast nodules than women are (8, 36).

The only study which compared the incidence of breast nodules in Depo-Provera users with incidence in controls found no significant difference between the two (98). McDaniel, who conducted the study with 1,270 users of the injectable and 257 controls, called the beagle experiments "unfortunate and misleading."

After Norigest was discovered to cause pituitary and breast nodules in rats, Schering AG stopped clinical trials (116) and removed the injectable from the market in Peru, the only country where it was available commercially (25).

Later studies revealed that in rats Norigest has strong estrogenic effects, rather than the progestational effects it has in rabbits and humans. Schering scientists postulate that this estrogenic effect in rodents causes pituitary proliferation and tumors and increases the secretion of prolactin by the pituitary. The increased prolactin overstimulates mammary growth and triggers the development of mutant cells. Because of species differences this does not occur in humans (116). To varying degrees, other nortestosterone derivatives also cause breast nodules in rodents. Because rodents appear to be inappropriate test animals, the USFDA has been willing to approve for human contraceptive use nortestosterone derivatives which have slight tumorigenic effects on rodents.

USFDA officials defend the agency's general reliance on animal studies with the rationale that, while evidence of tumorigenic effect in animals does not mean the drug will cause tumors in humans, evidence that it is *not* tumorigenic in animals allows a drug to be marketed with "a certain measure of assurance" of its safety for humans (8). They emphasize, however, that the agency's decisions are based on US conditions which may not apply in other countries:

> The risk-to-benefit principle alone is bound to vary from country to country, requiring variations in interpretations of results obtained in tests for toxicology, carcinogenicity and other multi-phased complexities arising from such investigations. Different interpretations and their consequent utilization by different agencies in different countries . . . must be made by the responsible agencies on their merits for prevailing conditions and in the best public interest (8).

PROGRAM ISSUES

The advantages of injectable progestogens—effectiveness, convenience, ease of administration, and lack of inhibition of lactation—make them popular with a large number of both users and clinicians. Nevertheless, the place of injectable progestogens in a comprehensive family planning program has not yet been fully determined. With lactating women or women whose families are complete, injectables may be both popular and appropriate, but, from the program planner's point of view, the overall effect could be the substitution of injectables for IUDs or sterilizations. With nulliparous women or those who want more children, many family planning officials still urge caution and limit the use of injectables.

Advantages . . .

From the users' point of view, injectables are attractive. Reports from family planning programs around the world show that, where women were offered a choice among contraceptive methods which included an injectable, between one-quarter and three-quarters chose the injectable (51, 74, 90, 125, 155, 172). Effectiveness, convenience, freedom from fear of forgetting (94), and the fact that husbands cannot interfere with its use (125) are major reasons for the popularity of the injectable (see Fig. 7). The mode of administration is also an asset. The attitude McDaniel and Pardthaisong found in Thailand holds true elsewhere as well (17, 51, 136):

Fig. 7. Advantages and Disadvantages of Injectable Progestogens Compared to Oral Contraceptives and IUDs.

Advantages of Injectables Compared to Orals

- More convenient to use. No daily pill taking.
- Freedom from fear of forgetting.
- No inhibition of lactation.
- No estrogen side effects or possible long-term hazards of estrogen.
- Husband cannot interfere with use.

Advantages of Injectables Compared to IUDs

- More effective.
- No pelvic examination or insertion procedure necessary.
- No risk of IUD side effects such as pain, perforations, or infections.
- Heavy bleeding less frequent.

Disadvantages of Injectables Compared to Orals

- Cannot be immediately withdrawn if harmful or distressing side effects occur.
- Greater possibility of disturbed menstrual patterns.
- Possible delay in return of fertility.
- Self-administration not practical.

Disadvantages of Injectables Compared to IUDs

- Need to return periodically for injections.
- Possibility of disturbed menstrual patterns.
- Possible delay in return of fertility.
- Carcinogenic issues still unresolved.

> . . . since the turn of the century, medicines given by needle and syringe have been widely regarded as more reliable, more effective, and more prompt in their actions than medicines taken orally. In the minds of many of the common people, a physician without a syringe is not a real physician at all, no matter how high his degree or other qualifications may be. Therefore a contraceptive to be taken by injection has a tremendous advantage over other methods (95).

An important advantage is that injectables do not inhibit lactation (43, 65, 183), as the estrogen-progestogen oral contraceptives sometimes do (10, 79, 82). In fact, the injectables may actually increase both the duration of lactation (43, 45) and the volume of milk (47, 65, 80). They are therefore preferable to oral contraceptives for postpartum use, especially in countries where mothers breastfeed their children for long periods (47).

An effective steroidal contraceptive which does not reduce lactation is welcome for two reasons. Firstly, in the postpartum period women are highly motivated to accept contraception (191, 192). Secondly, contrary to popular thought, ovulation and conception can occur before the end of lactation amenorrhea (170). Furthermore, in areas where a woman's only access to medical care and advice is during childbirth, a single injection at that time can provide her with several months of protection against the next pregnancy (76). In an extensive review of the duration and contraceptive effect of lactation, Dr. Franz Rosa of the UN Fund for Population Activities (UNFPA) has recommended that progestogen-only contraceptives be provided to lactating women at least until menstruation recommences (138).

Whether injectable progestogens alter the composition of breast milk is uncertain. While one research group found no significant differences in specific gravity, protein content, and fat content between the milk of Depo-Provera users and that of controls (80), another group reported significantly higher milk protein levels and decreased milk lipid and lactose levels (47). The injectable progestogens apparently do not affect the immunologic powers of breast milk (27).

Depo-Provera and/or its by-products (metabolites) can be found in the breast milk of women using the injectable (78), but whether this can affect an infant has not been determined. Radioimmunoassays, used to test for the presence of steroids in breast milk, cannot distinguish between the drug and its metabolites, and it is not known whether the metabolites are physiologically active. There have been no clinical reports of adverse effects on infants whose mothers were receiving progestogens, but additional research is needed on this point.

In a family planning program injectables offer the advantage of quick, easy, and infrequent administration. McDaniel has found that, if a woman returning for an injection has no complaints, she can be processed in 60 to 90 seconds. This includes time for a short interview with a doctor or nurse-midwife, paperwork, and the injection itself (95). Dispensing both Depo-Provera and oral contraceptives, one of McCormick Hospital's mobile family planning clinics routinely serves 800 women in one day and 1,500 in the next on two stops near Thailand's border with Burma (93) (see Fig. 8). The six-month regimen saves even more clinic time and resources, but it provides a woman less contact with health personnel should questions or problems arise.

The injectable progestogens can be administered by jet injector (126, 143), and evidence from animal studies indicates that use of the jet may reduce the variation from one woman to the next in the return of fertility after discontinuation (177). Both Depo-Provera and Norigest can be stored without refrigeration for up to five years.

Like oral contraceptives, the injectables have a great potential for wider distribution and use. Paramedical personnel can easily give injections. Dropping the requirement that a woman have a pelvic examination before starting an injectable would also broaden its acceptance in many areas, since some women will refuse to seek contraception if pelvic or general physical exams are required (86, 139). In developing countries the benefits of wider distribution of both injectable and oral contraceptives, especially in terms of the potential reduction expected in maternal mortality rates, outweigh the risks (139) (see **Population Report** A-2). For these reasons McDaniel does not require pelvic exams in his Thailand program.

> *We* feel that furnishing family planning services to a large number of women, without the "luxuries" of general physical and pelvic examinations and cancer detection, is more important and fruitful than *serving a few*, and *discouraging many*, in an attempt to cling too rigidly to more academic and professional medical standards (91).

Fig. 8. Women receive numbered tickets to wait in turn for Depo-Provera injections or oral contraceptives from a McCormick Hospital mobile clinic in Chiang Mai Province, Thailand. (Courtesy of Dr. E. B. McDaniel.)

. . . But Use Restricted

Despite the advantages of injectables, many family planning officials have been reluctant to permit the unrestricted use of Depo-Provera. They have been concerned because the drug could not be withdrawn quickly if a problem arose, although this has not proved a problem in actual practice (94). More importantly, they have feared that Depo-Provera might cause permanent infertility. There has been no proof that injectables can cause sterility, and, if they do, it occurs very rarely. But officials and clinicians are aware not only that undesired infertility could have disastrous emotional and social consequences for the woman involved, but also that the reputation of a family planning program and of family planning itself could be ruined if people thought they had been deceived about the reversibility of the method. Thus, even in countries such as Jamaica, Malaysia, and Thailand, where Depo-Provera is now offered through national family planning programs, restrictions have been placed on its use. In Jamaica, only women whose families are complete may obtain Depo-Provera. The World Health Organization (WHO) has imposed the same restriction on Depo-Provera supplied by UNFPA. The International Planned Parenthood Federation (IPPF), though still without an official policy, unofficially advises its affiliates against giving Depo-Provera to young women with few children (139). In Nairobi, the Family Welfare Center, which obtains Depo-Provera from IPPF, restricts the injectable to women over 30 with five or more children and to those who, with their husbands, sign consent forms (51).

In the Thai National Family Planning Program, a woman using Depo-Provera must have at least two living children and want no more. If, after using the injectable for "a period of time," she still wants no more children, she will be urged to discontinue the injectable and to accept sterilization. The Thai National Ministry of Health hopes that Depo-Provera, a recent addition to the national program, will attract new participants to family planning

Table 5—Usage of Depo-Provera Reported by Family Planning Associations Supplied by the International Planned Parenthood Federation, 1971-74, and Planned IPPF Deliveries, 1975

Region	Usage 1971	Usage 1972	Usage 1973	Estimated Usage 1974	To Be Delivered 1975
Africa	7,140	22,526	106,768	129,130	241,000
Indian Ocean	2,128	9,157	13,030	38,360	77,000
Middle East & North Africa	0	100[a]	4,055	7,000	13,000
South East Asia & Oceania	28,460[b]	53,300[c]	83,017	161,874	177,000
Western Hemisphere	20,331	22,421	35,382	45,932	114,100
Western Pacific[d]	21,519	23,338	23,082	18,000	18,000
TOTAL	79,578	130,842[c]	265,334	400,296	640,100

[a]Sudan only. [b]Thailand only. [c]Approximate. [d]Hong Kong only.
SOURCES: IPPF Reports to Donors (56,57,58).

rather than draw women away from sterilization procedures, the number of which has been rapidly increasing recently. Depo-Provera is currently available only at National Family Planning Program hospitals and health centers staffed by physicians—some 300 out of about 4,000 program outlets (180). However, a study has been started to evaluate the use of auxiliary midwives to prescribe and administer the drug.

The McCormick Hospital program in Chiang Mai, Thailand, which was one of the first to offer Depo-Provera, takes a less stringent approach. The only requirement for new acceptors of Depo-Provera is that they have demonstrated their fertility by a previous pregnancy. McDaniel, who directs the program, reports that this requirement "is only to protect the reputation of the program from the accidental giving of Depo-Provera to an already sterile couple" (94).

In Malaysia national family planning officials also have restricted Depo-Provera. The injectable is available through 10 National Family Planning Board (NFPB) clinics with attending medical officers to women who have "already demonstrated their fertility" and have completed their families. The NFPB requires that women receive physical and pelvic examinations before starting Depo-Provera and checks for breast nodules with every injection. Also, they must be told individually about all possible side effects, including menstrual cycle disruption and "possible infertility" (132).

Had USFDA approval of Depo-Provera gone into effect, it would have placed special requirements on the use of the injectable in the USA. In its approval statement the agency wrote that Depo-Provera was intended for "those patients in need of contraception who cannot accept more regimented methods or in whom other alternatives are either contraindicated, unreliable, or otherwise unacceptable." Before a woman could have received her first injection, she would have had to give her consent after reading a brochure which explained the known and suspected side effects and risks of Depo-Provera. Also, pharmacies, private doctors, and family planning clinics would have been required to report back to the Upjohn Company on their distribution or use of Depo-Provera. If harmful effects were later discovered, the company then would have been able to notify doctors, who in turn would have contacted their patients (146). Because USFDA approval never took effect, these requirements were never instituted.

Fig. 9. Partial List of Countries Where Depo-Provera is Available as a Contraceptive Through Commercial Channels and/or Family Planning Programs, 1974-1975

Some countries where Depo-Provera for contraception is available:

Western Hemisphere:

Argentina	Grenada	Peru
Barbados	Guatemala	St. Kitts
Bolivia	Honduras	St. Lucia
Chile	Jamaica	St. Vincent
Colombia	Mexico	Surinam
Costa Rica	Panama	Trinidad
El Salvador	Paraguay	

Middle East & Africa:

Afghanistan	Lebanon	Seychelles
Botswana	Liberia	Sierra Leone
Egypt	Lesotho	South Africa
Gambia	Malagasy	Sudan
Ghana	Mauritius	Tanzania
Iraq	Nigeria	Tunisia
Iran	Rhodesia	Uganda
Kenya	Saudi Arabia	

Far East, South Asia & Pacific:

Bangladesh	Malaysia	Philippines
Hong Kong	New Zealand	Pakistan
Indonesia	Sabah	Thailand
Khmer Republic	Sarawak	Vietnam
Korea	Sri Lanka	

Europe:

Belgium	Federal Republic of Germany	Netherlands
Denmark		Spain

Some countries where Depo-Provera for contraception is not available:

Brazil	Japan	United States
Canada	Sweden	Venezuela
India	United Kingdom	

SOURCES: Heywood (49,50); IPPF (58); Nortman & Hofstatter (116).

DISTRIBUTION

Despite caution and restrictions on Depo-Provera, its use has grown in recent years. At least 10 countries now offer the injectable in their national family planning programs, and use for contraceptive purposes has been approved in 64 countries. Two international donor organizations, IPPF and UNFPA, now supply Depo-Provera, but the US Agency for International Development (USAID) does not, since it does not supply drugs which have not been approved by the USFDA for use in the USA.

IPPF is currently the largest international supplier of injectable contraception. In 1975 IPPF plans to provide approximately 640,000 three-month doses of Depo-Provera to family planning clinics in 41 countries (58). This could provide one year of contraception for almost 150,000 women (124). Requests to IPPF for Depo-Provera have grown rapidly over the past several years, both in terms of the number of programs requesting the injectable and the amounts requested (see Table 5). The largest IPPF shipments in 1974 went to Thailand (140,000 three-month doses), Sri Lanka (35,000 doses), Uganda (12,000 doses), Kenya and Costa Rica (10,000 doses each) (58).

UNFPA began supplying small quantities of Depo-Provera in 1972. In 1972 and 1973 UNFPA shipments ranged from 220 to 10,000 doses and went to six countries (19). In 1974, at a cost of $.71 (US) per three-month dose, UNFPA ordered $200,000 (US) worth of Depo-Provera for Thailand, $38,000 (US) worth for Jamaica, and $600,000 (US) worth to be turned over to IPPF for distribution to its affiliates (19, 137).

UNFPA has set aside a small portion of its 1975 contraceptive supplies budget—up to $200,000 (US) out of almost $4 million—to buy either Depo-Provera or, if WHO gives its approval, Noristerat (Norigest), depending upon which manufacturer submits the lower bid price.

The Swedish International Development Authority (SIDA) has supplied injectable contraception only once, and it does not plan to do so again because of reservations about side effects. In 1974 SIDA provided 100,000 three-month doses of Depo-Provera to Malaysia's national family planning program (164). In 1975 and coming years, the Malaysia National Family Planning Board intends to obtain its supply of injectables from UNFPA (132).

National family planning programs which offer Depo-Provera include those in Jamaica, Guatemala, Thailand, Malaysia, Hong Kong, Khmer Republic (Cambodia), Botswana, South Africa, Rhodesia, and Uganda. The fees for injections which these programs charge to users vary. In Jamaica, for example, injections, like all other contraceptive supplies, are free. In Hong Kong in 1974 the fee ranged from no charge to $1.40 (US) per injection, depending on ability to pay. Other fees per injection in 1974, expressed in US dollars, included: Botswana, $.43; Guatemala, $.50; Khmer Republic, $.30; Rhodesia, $.41; and Uganda, $.70 (121). The new Thai pilot program charges a service fee of $.75 for each injection, as does the McCormick Hospital program (94).

Total Depo-Provera Sales

Through commercial channels and sales to international donors, the Upjohn Company has sold close to 11 million doses of Depo-Provera since 1968. The company's Belgian affiliate, Upjohn S.A. Purrs, manufactures the drug for international distribution. Upjohn affiliates in Colombia, Mexico, Korea, the Philippines, South Africa, and Argentina produce Depo-Provera for use within their own countries but do not ship to other nations. The drug is now commercially available as a "contraceptive," "anovulatory agent," or "anti-conception compound" in 64 nations, including 19 Western Hemisphere countries, 13 Middle East countries, 17 African, 8 European, and 7 Far East countries (49) (see Fig. 9).

Though doubts have clouded the history of injectable progestogens and important questions remain unanswered, use of Depo-Provera has grown in recent years. Barring conclusive proof that the injectables cause cancer, their use probably will continue growing. In fact, injectables may become the first contraceptives produced by modern technology to win acceptance in the developing countries while lacking approval in most major industrialized nations.

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